

PCT

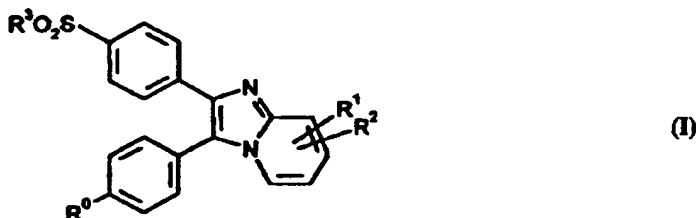
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>C07D 471/04, A61K 31/435 // (C07D 471/04, 235:00, 221:00)</b>		A1	(11) International Publication Number: <b>WO 96/31509</b> (43) International Publication Date: <b>10 October 1996 (10.10.96)</b>
(21) International Application Number: <b>PCT/EP96/01438</b>			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: <b>2 April 1996 (02.04.96)</b>			
(30) Priority Data: 9506965.4 4 April 1995 (04.04.95) GB 9512099.4 14 June 1995 (14.06.95) GB 9516117.0 5 August 1995 (05.08.95) GB			
(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			Published With international search report.
(72) Inventors; and (75) Inventors/Applicants (for US only): BESWICK, Paul, John [GB/GB]; Glaxo Research and Development Limited, Gunnels Wood Road, Stevenage, Herts. SG1 2NY (GB). CAMPBELL, Ian, Baxter [GB/GB]; Glaxo Research and Development Limited, Gunnels Wood Road, Stevenage, Herts. SG1 2NY (GB). NAYLOR, Alan [GB/GB]; Glaxo Research and Development Limited, Gunnels Wood Road, Stevenage, Herts. SG1 2NY (GB).			
(74) Agent: LANE, Graham, M., H.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			

(54) Title: IMIDAZO[1,2-a]PYRIDINE DERIVATIVES



(57) Abstract

The invention provides the compounds of formula (I) and pharmaceutically acceptable derivatives thereof in which: R<sup>0</sup> represents halogen; R<sup>1</sup> and R<sup>2</sup> are independently selected from H, halogen, C<sub>1</sub>-alkyl, C<sub>1</sub>-alkyl substituted by one or more fluorine atoms, C<sub>1</sub>-alkoxy, C<sub>1</sub>-hydroxyalkyl, SC<sub>1</sub>-alkyl, C(O)H or C(O)C<sub>1</sub>-alkyl; and R<sup>3</sup> represents C<sub>1</sub>-alkyl. Compounds of formula (I) are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever, inflammation of a variety of conditions and diseases.

Atty. Docket No. 6794S-5/US/USC  
Serial No. 10/031,898  
Kararli, et al.  
Reference 59 of 69

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

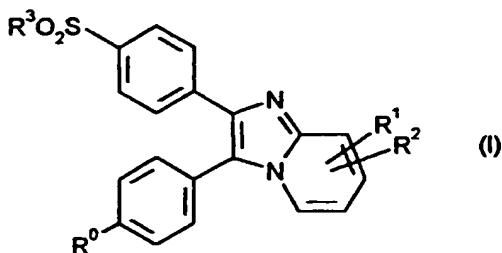
AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroun	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## IMIDAZO[1,2-a] PYRIDINE DERIVATIVES

This invention relates to imidazo[1,2-a]pyridine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

5      The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1. We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2.

10     20     The invention thus provides the compounds of formula (I)



and pharmaceutically acceptable derivatives thereof in which:

R<sup>0</sup> represents halogen;

R<sup>1</sup> and R<sup>2</sup> are independently selected from H, halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted by one or more fluorine atoms, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>hydroxyalkyl, SC<sub>1-4</sub>alkyl, C(O)H or C(O)C<sub>1-4</sub>alkyl; and

R<sup>3</sup> represents C<sub>1-4</sub>alkyl.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate or ester, or salt or solvate of such ester, of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

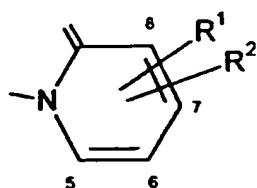
It will be appreciated that, for pharmaceutical use, the salts referred to above will be the physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiologically acceptable salts thereof.

10 Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids, preferably inorganic acids, e.g. hydrochlorides, hydrobromides and sulphates.

The term halogen is used to represent fluorine, chlorine, bromine or iodine.

15 The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

The substituents R<sup>1</sup> and R<sup>2</sup> may be at the 5-, 6-, 7- or 8- positions of the pyridine ring of formula (I), as defined hereinbelow:



20 Preferably, R<sup>1</sup> is at the 8- position; and R<sup>2</sup> is at the 7- position or, when R<sup>1</sup> is other than H, the 5-, 6- or 7-position. More preferably, R<sup>1</sup> is at the 8- position; and R<sup>2</sup> is at the 7- position or, when R<sup>1</sup> is C<sub>1</sub>-alkyl (e.g. methyl), the 5- or 7- position.

Preferably, R<sup>0</sup> represents fluorine.

25 Preferably, R<sup>1</sup> represents H, chlorine, bromine, C<sub>1</sub>-alkyl (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g. CH<sub>2</sub>F or CF<sub>3</sub>), C<sub>1</sub>-hydroxyalkyl

(e.g.  $\text{CH}_2\text{OH}$  or  $\text{CH}(\text{OH})\text{CH}_3$ ),  $\text{SC}_{1-4}\text{alkyl}$  (e.g.  $\text{SCH}_3$ ),  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$  (e.g.  $\text{C}(\text{O})\text{CH}_3$ ). More preferably,  $\text{R}^1$  represents H, chlorine, bromine, methyl,  $\text{CH}_2\text{F}$ ,  $\text{CF}_3$ ,  $\text{SCH}_3$ ,  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{CH}_3$ . Most preferably  $\text{R}^1$  represents  $\text{C}(\text{O})\text{CH}_3$ .

5 Preferably,  $\text{R}^2$  represents H, chlorine, bromine, or  $\text{C}_{1-4}\text{alkyl}$  (e.g. methyl). More preferably,  $\text{R}^2$  represents H, bromine or methyl.

Preferably,  $\text{R}^3$  represents methyl.

10 Within the invention there is provided one group of compounds of formula (I) (group A) wherein:  $\text{R}^0$  represents fluorine;  $\text{R}^1$  represents H, chlorine, bromine,  $\text{C}_{1-4}\text{alkyl}$  (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g.  $\text{CH}_2\text{F}$  or  $\text{CF}_3$ ),  $\text{C}_{1-4}\text{hydroxyalkyl}$  (e.g.  $\text{CH}_2\text{OH}$  or  $\text{CH}(\text{OH})\text{CH}_3$ ),  $\text{SC}_{1-4}\text{alkyl}$  (e.g.  $\text{SCH}_3$ ),  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$  (e.g.  $\text{C}(\text{O})\text{CH}_3$ );  $\text{R}^2$  represents H, chlorine, bromine, or  $\text{C}_{1-4}\text{alkyl}$  (e.g. methyl); and  $\text{R}^3$  represents methyl.

15 Within group A there is provided the sub-group of compounds wherein:  $\text{R}^0$  represents fluorine;  $\text{R}^1$  represents H, chlorine, bromine, methyl,  $\text{CH}_2\text{F}$ ,  $\text{CF}_3$ ,  $\text{SCH}_3$ ,  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{CH}_3$ ;  $\text{R}^2$  represents H, bromine or methyl; and  $\text{R}^3$  represents methyl.

20 Within the invention there is provided another group of compounds of formula (I) (group B) wherein  $\text{R}^0$  represents fluorine;  $\text{R}^1$  is at the 8- position and represents H, chlorine, bromine,  $\text{C}_{1-4}\text{alkyl}$  (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g.  $\text{CH}_2\text{F}$  or  $\text{CF}_3$ ),  $\text{C}_{1-4}\text{hydroxyalkyl}$  (e.g.  $\text{CH}_2\text{OH}$  or  $\text{CH}(\text{OH})\text{CH}_3$ ),  $\text{SC}_{1-4}\text{alkyl}$  (e.g.  $\text{SCH}_3$ ),  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$  (e.g.  $\text{C}(\text{O})\text{CH}_3$ );  $\text{R}^2$  is at the 7- position or, when  $\text{R}^1$  is other than H, the 5-, 6- or 7- position, and represents H, chlorine, bromine, or  $\text{C}_{1-4}\text{alkyl}$  (e.g. methyl); and  $\text{R}^3$  represents methyl.

25 Within group B there is provided the sub-group of compounds wherein:  $\text{R}^0$  represents fluorine;  $\text{R}^1$  is at the 8- position and represents H, chlorine, bromine, methyl,  $\text{CH}_2\text{F}$ ,  $\text{CF}_3$ ,  $\text{SCH}_3$ ,  $\text{C}(\text{O})\text{H}$  or  $\text{C}(\text{O})\text{CH}_3$ ;  $\text{R}^2$  is at the 7- position or, when  $\text{R}^1$  is methyl, the 5- or 7- position, and represents H, bromine or methyl; and  $\text{R}^3$  represents methyl.

30 Within the invention there is provided a further group of compounds of formula (I) (group C) wherein  $\text{R}^0$  represents fluorine;  $\text{R}^1$  is at the 8- position and

represents H, chlorine, bromine,  $C_{1-4}$ alkyl (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g.  $CH_2F$  or  $CF_3$ ),  $C_{1-4}$ hydroxyalkyl (e.g.  $CH_2OH$  or  $CH(OH)CH_3$ ),  $SC_{1-4}$ alkyl (e.g.  $SCH_3$ ),  $C(O)H$  or  $C(O)C_{1-4}$ alkyl (e.g.  $C(O)CH_3$ );  $R^2$  represents H; and  $R^3$  represents methyl.

5 Within group C there is provided the sub-group of compounds wherein:  $R^0$  represents fluorine;  $R^1$  is at the 8- position and represents H, chlorine, bromine, methyl,  $CH_2F$ ,  $CF_3$ ,  $CH(OH)CH_3$ ,  $SCH_3$ ,  $C(O)H$  or  $C(O)CH_3$ ;  $R^2$  represents H; and  $R^3$  represents methyl.

10 Within the above groups (and preferred groups) of compounds, especially preferred groups of compounds are those wherein  $R^1$  represents  $C(O)CH_3$ .

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

15 Preferred compounds of the invention are:  
3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine;  
3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine;  
3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-trifluoromethyl-imidazo[1,2-a]pyridine;  
20 3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-7-methyl-imidazo[1,2-a]pyridine;  
8-chloro-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine;  
3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methanesulfanyl-imidazo[1,2-a]pyridine;  
25 8-bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine;  
8-fluoromethyl-3-(4-fluoro-phenyl)-2-(4-methanesulphonyl-phenyl)-imidazo[1,2-a]pyridine;  
30 3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-7,8-dimethyl-imidazo[1,2-a]pyridine;  
3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine-8-carbaldehyde;

5-bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine;  
6-bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine;  
5 [3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-methanol;  
(±) 1-[3-(4-fluoro-phenyl)-2-(4-methanesulphonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-ethan-1-ol;  
and pharmaceutically acceptable derivatives thereof.

10 A particularly preferred compound of the invention is:  
8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine; and pharmaceutically acceptable derivatives thereof.

Compounds of the invention are potent and selective inhibitors of COX-2. This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1.

15 In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain, fever and inflammation of a variety of conditions and diseases. Such conditions and diseases are well known in the art and include rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; neuralgia; synovitis; arthritis, including 20 rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and 25 those arising from surgical and dental procedures.

The compounds of the invention may also be useful for the treatment of other conditions mediated by selective inhibition of COX-2.

30 For example, the compounds of the invention may inhibit cellular and neoplastic transformation and metastatic tumour growth and hence be useful in the treatment of certain cancerous diseases, such as colonic cancer.

Compounds of the invention may also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore

may be of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures).

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence may be of use in the treatment of dysmenorrhoea and 5 premature labour.

Compounds of the invention inhibit inflammatory processes and therefore may be of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, 10 Chron's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

15 Compounds of the invention may also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

Compounds of the invention may also be useful for the treatment of cognitive 20 disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions 25 (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

30 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by selective inhibition of COX-2.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative.

5

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of inflammatory disorders.

10

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

15

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

20

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include pain relievers such as a glycine antagonist, a sodium channel inhibitor (e.g. lamotrigine), a substance P antagonist (e.g. an NK<sub>1</sub> antagonist), acetaminophen or phenacetin; a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor (e.g. an iNOS or an nNOS inhibitor); an inhibitor of the release, or action, of tumour necrosis factor  $\alpha$ ; an antibody therapy (e.g. a monoclonal antibody therapy); a stimulant, including caffeine; an H<sub>2</sub>-antagonist, such as ranitidine; an antacid, such as aluminium or magnesium hydroxide; an antiflatulent, such as simethicone; a decongestant, such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive, such as codeine, hydrocodone, carmiphen, carbetapentane, or dextromethorphan; a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention covers the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in combination with one or more other therapeutic agents.

25

30

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example

subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

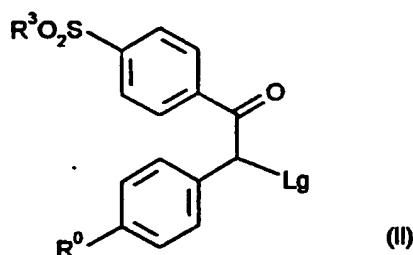
When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01 mg/kg to 500 mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

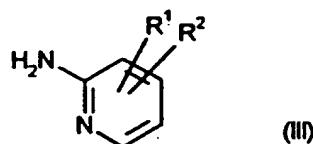
Compounds of formula (I) and pharmaceutically acceptable derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure.

5 Suitable methods for the preparation of compounds of formula (I) and pharmaceutically acceptable derivatives thereof are described below. In the formulae that follow  $R^0$  to  $R^3$  are as defined in formula (I) above unless otherwise stated and  $Lg$  represents a leaving group, such as a sulphonate (e.g. methanesulphonate) or a halogen (e.g. bromine).

Thus according to a first process (A), compounds of formula (I) may be prepared by reacting a compound of formula (II)



or a protected derivative thereof with a compound of formula (III)



10

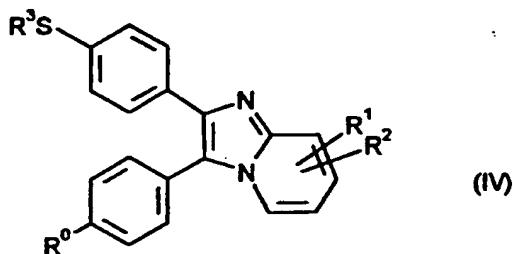
or a protected derivative thereof. The reaction is conveniently carried out in a solvent, such as a polar solvent (e.g. acetonitrile or isopropanol); at elevated temperature, e.g. reflux; and optionally in the presence of a base, such as an alkali metal bicarbonate or carbonate (e.g. potassium carbonate).

15

Suitable leaving atoms or groups in respect of  $Lg$  in formula (II) are described in many standard texts on organic chemistry, for example in table 10.10 on page 357 of 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992). It will be appreciated by a person skilled in the art that the choice of a particular leaving group in the above reaction may depend upon the meanings of  $R^0$  to  $R^3$  (and hence the compound of formula (I) desired) and the reaction conditions employed.

20

According to another process (B), compounds of formula (I) may be prepared by reacting a compound of formula (IV)



5 or a protected derivative thereof with an oxidising agent. Conveniently the oxidation is effected using a monopersulfate compound, such as potassium peroxyomonosulfate (known as Oxone<sup>TM</sup>) and the reaction is carried out in a solvent, such as an aqueous alcohol, (e.g. aqueous methanol), and at between -78°C and ambient temperature.

10 According to another process (C) compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors.

15 Thus, for example, compounds of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent chlorine, bromine or iodine may be prepared from the corresponding compound of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent H, by treatment with an appropriate halogenating agent (i.e. chloro-, bromo- or iodinating agent). Suitable agents include the corresponding N-halosuccinimides. Conveniently the reaction is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. chloroform), and at ambient temperature.

20 Compounds of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent C<sub>1</sub>-alkyl substituted by one or more fluorine atoms may be prepared from the compound of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represents the corresponding C<sub>1</sub>-hydroxyalkyl by treatment with a suitable source of fluorine. Suitable sources of fluorine include, for example, diethylaminosulphur trifluoride. Conveniently the reaction is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. dichloromethane), and at reduced temperature, such as -78°C.

25 Compounds of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent C(O)H may be prepared from the corresponding compound of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent CH<sub>2</sub>OH by oxidation. Suitable oxidising agents include, for example,

manganese (IV) oxide. Conveniently the oxidation is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. chloroform), and at elevated temperature (e.g. reflux).

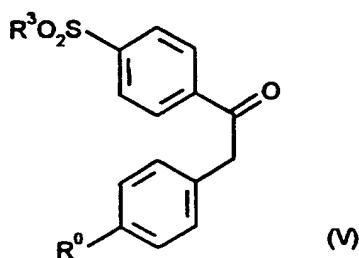
Compounds of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent C<sub>1-4</sub>hydroxyalkyl, and wherein the hydroxy group is attached to the carbon linked to the pyridine ring, may be prepared by reduction of the compound of formula (I) wherein R<sup>1</sup> or R<sup>2</sup> represent the corresponding aldehyde or ketone. Suitable reducing agents include hydride reducing agents, such as diisobutylaluminium hydride. Conveniently the reduction is effected in the presence of a solvent, such as a halogenated hydrocarbon (e.g. dichloromethane), and at reduced temperature, such as -78°C.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the above described processes to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

Another process (D) for preparing compounds of formula (I) thus comprises deprotecting protected derivatives of compounds of formula (I).

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Green, second edition, (John Wiley and Sons, 1991), which also describes methods for the removal of such groups.

Compounds of formula (II) may be prepared from compounds of formula (V)



by conventional means.

Thus, compounds of formula (II) wherein Lg represents a halogen may be

prepared from compounds of formula (V) by treatment with a halogenating agent, at reduced temperature and in a solvent, such as a chlorinated hydrocarbon. For example, where Lg represents bromine, the reaction is conveniently effected with a brominating agent, such as bromine in the presence of a strong acid (e.g. hydrobromic acid in acetic acid).

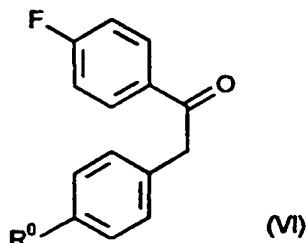
5

Compounds of formula (II) wherein Lg represents a sulphonate may be prepared from compounds of formula (V) firstly by oxidation to the corresponding  $\alpha$ -hydroxy ketone, followed by treatment with a sulphonating agent. Suitable oxidising agents include, for example,  $\text{Pb}(\text{OAc})_4$ , 10 dimethyldioxirane and those described in *F A Davis, J. Org. Chem., 1984, 49(17), 3284*. Suitable sulphonating agents include sulphonylhalides, such as sulphonylchlorides (e.g. methanesulphonylchloride). The sulphonylation is conveniently effected in the presence of a base, such as an amine (e.g. triethylamine); and in a solvent, such as a halogenated hydrocarbon.

10

15

Compounds of formula (V) may be prepared from compounds of formula (VI)



20

by treatment with an alkali sulphinate, such as a sodium sulphinate. Conveniently, the reaction is carried out in a polar solvent, such as dimethyl sulphoxide, and at elevated temperature.

25

Compounds of formula (III) are either known compounds or may be prepared by literature methods such as those described in, for example, *J A Turner, J. Org. Chem., 1983, 48, 3401*; *M Malinowski, Bull. Soc. Chim. Belg., 1988, 97, 51*; *W O Siegl, J. Het. Chem., 1981, 18, 1613-18*; or *F Trecourt et al, J. Chem. Soc., Perkin Trans. 1 1990, 9, 2409-2415*.

Compounds of formula (VI) are either known compounds or may be prepared by literature methods such as those described in, for example, *N Seko et al, Chem. Pharm. Bull., 1991, 39, (3), 651-7*, or *I Lalazor et al, J. Med. Chem. 1971, 14,*

1138-40.

Compounds of formula (IV) or protected derivatives thereof may be prepared using conventional chemistry, for example chemistry analogous to that herein described for the preparation of compounds of formula (I).

5 Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formula (II) and (IV) are key intermediates and represent particular aspects of the present invention.

10 Conveniently, compounds of the invention are isolated following work-up in the form of the free base. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means.

15 Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Flash chromatography was carried out using Merck 9385 silica. Thin layer chromatography (Tlc) was carried out on silica plates. NMR was carried out on a Brucker 300Mhz spectrometer, using CDCl<sub>3</sub> as solvent. Chemical shifts are given in δ ppm with respect to tetramethylsilane as internal chemical shift reference. The following 20 abbreviations are used: Et = ethyl, s = singlet, d = doublet, t = triplet and m = multiplet.

Intermediate 1

2-(4-Fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone

25 A mixture of the 2-(4-fluoro-phenyl)-1-(4-fluoro-phenyl)-ethanone<sup>1</sup> (3g) and sodium methane sulphinate (1.58g) in dry dimethyl sulphoxide (10ml) was heated to 105-110° under nitrogen for 18h. The cooled reaction mixture was poured into water (500ml) and the mixture extracted with ethyl acetate. The combined organic extracts were adsorbed onto silica and purified by flash chromatography eluting with ethyl acetate:hexane (1:1) to give the title 30 compound as a white solid (2.1g).

m.p. 115-116°

<sup>1</sup> Ref: I Lalazor et al, J.Med.Chem. 1971, 14, 1138-40.

Intermediate 22-Bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone

A solution of the 2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone (1.6g) in dichloromethane (30ml) and glacial acetic acid (15ml) was cooled to 0° and treated with 48% hydrobromic acid (3 drops). A solution of bromine (875mg) in acetic acid (2ml) was added and stirring continued for 4 hours. The mixture was diluted with dichloromethane (35ml) and the solution was washed with water, dried, and concentrated to give the title compound as a yellow solid (2.0g).

10 m.p. 124-126°

Intermediate 33-Trifluoromethyl-pyridin-2-ylamine

A mixture of 2-chloro-3-trifluoromethyl-pyridine (5g), copper(1) iodide (5g) and liquid ammonia (50ml) was heated in an autoclave at 80° (internal temperature) for 28 hours. The cooled reaction mixture was slurried with methanol/chloroform (1/1-250 ml) and filtered. The filtrate was absorbed onto silica and purified by flash chromatography eluting with ethyl acetate/hexane (1/1), to yield the title compound as a white solid (1.4g).

m.p. 71-72°

20  $MH^+ = 163$

Tlc  $SiO_2$ , Rf 0.50 (ethyl acetate/hexane (1/1)) detection UV/KMnO<sub>4</sub>

Intermediate 42-(4-Fluoro-phenyl)-1-(4-methanesulfanyl-phenyl)-ethanone

A mixture of 2-(4-fluoro-phenyl)-1-(4-fluoro-phenyl)-ethanone (10.0g) sodium methanethiolate (3.0g) and dimethyl sulphoxide (10ml) was heated at ~100° for 8h under nitrogen. The cooled mixture was added to water (250ml), stirred for 10 min and filtered. The resulting solid was crystallised from isopropanol (100ml) twice to give the title compound as a white solid (5.0g).

m.p. 143-144°

30 Intermediate 5

2-Bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfanyl-phenyl)-ethanone

A solution of 2-(4-fluoro-phenyl)-1-(4-methanesulfanyl-phenyl)-ethanone (4.8g) in dichloromethane (75ml) and acetic acid (30ml) at 0° containing 48% HBr (15 drops) was treated dropwise with bromine (2.6g), in acetic acid (6ml). The

solution was stirred at 0° for 10 min and at room temperature for 3h, diluted with dichloromethane (100ml) and washed with water (2 x 100ml). The dried ( $MgSO_4$ ) organic phase was evaporated and the residue was triturated with diethyl ether (30ml) to give the title compound as a white solid (4.5g).

5 m.p. 117-119°.

Tlc  $SiO_2$  ( $Et_2O$ :hexane 1:1) Rf 0.6 det u.v.  $KMnO_4$ , isopropanol.

Intermediate 6

3-(4-Fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine

10 A solution of 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfanyl-phenyl)-ethanone (4.0g) and 2-aminopyridine (1.2g) in acetonitrile (25ml) was refluxed under nitrogen for 2h and left at room temperature for 16h. The solution was evaporated and the residue purified by flash column chromatography eluting with diethyl ether (applied in  $CH_2Cl_2$ ) to give the title compound as a white solid (1.6g).

15 m.p. 115-118°

Tlc  $SiO_2$  ( $Et_2O$ ) Rf 0.5 det u.v., isopropanol.

Intermediate 7

8-Chloro-3-(4-fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine

20  $n$ -Butyllithium in hexane (1.6m; 0.35ml) was added dropwise to a solution of 3-(4-fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine (167mg) in tetrahydrofuran (2ml) at -78° under nitrogen. The solution was stirred at -78° for 1h and was treated with hexachloroethane (142mg) in tetrahydrofuran (0.25ml). The solution was allowed to warm to room temperature during 30 min and water (2ml) was added. The mixture was extracted with ethyl acetate (2 x 5ml) and the dried ( $MgSO_4$ ) extract was evaporated to give the title compound as a cream solid (180mg).

25 m.p. 148-149°

$MH^+$  = 369

30 Intermediate 8

3-Methylsulfanyl-pyridin-2-ylamine

A solution of 2,2-dimethyl-N-pyridin-2-yl-propionamide<sup>2</sup> (890mg) in dry tetrahydrofuran (30ml) was cooled to -78° and treated with a solution of  $n$ -butyl lithium (6.25 ml, 1.6M). This solution was stirred at 0° for 4 hours and a solution

of dimethyldisulphide (235mg) in tetrahydrofuran (5ml) was added and stirring continued at ambient temperature for 30 minutes. 2N Hydrochloric acid (1ml) was added and the solution concentrated *in vacuo*. A mixture of the residue and 2N hydrochloric acid (15ml) was heated at reflux for 4 hours. The cooled reaction mixture was made basic by addition of solid potassium carbonate. The basic mixture was extracted with ethyl acetate (15ml), the organic extract was dried ( $\text{Na}_2\text{SO}_4$ ) and absorbed onto silica. The title compound was obtained by flash chromatography eluting with ethyl acetate/cyclohexane (1/1) as a colourless oil (490mg).

10  $\text{MH}^+ = 141$

Tlc,  $\text{SiO}_2$ , Rf 0.48, (ethyl acetate/cyclohexane(1/1)) detection u.v.,  $\text{KMnO}_4$

<sup>2</sup> Ref: J A Turner J. Org. Chem. 1983, 48, 3401

#### Intermediate 9

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic acid methyl ester

A solution of 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone (700mg), and 2-amino-nicotinic acid methyl ester (287mg) in dry acetonitrile was heated at reflux overnight. The reaction mixture was concentrated onto silica and the title compound obtained by flash chromatography eluting with ethyl acetate:cyclohexane 5:1 as a yellow solid (176mg).

20  $\text{MH}^+ = 425$

Tlc,  $\text{SiO}_2$  Rf 0.21 (ethyl acetate:cyclohexane 5:1) detection uv

#### Intermediate 10

8-Acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine

n-Butyllithium in hexane (1.6m; 0.5ml) was added dropwise to a solution of 3-(4-fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine (250mg) in tetrahydrofuran (3ml) at -78° under nitrogen. The solution was stirred at -78° for 1h and was treated with N-methyl,N-methoxyacetamide (90mg) in tetrahydrofuran (0.25ml). The solution was allowed to warm to room temperature during 60min and water (10ml) was added. The mixture was extracted with ethyl acetate (2 x 5ml) and the dried ( $\text{MgSO}_4$ ) extract was

evaporated. The residue was purified on a column of silica, eluting with hexane:diethylether (3:1) to give the title compound as a cream solid (130mg).

$MH^+ = 377$

Tlc  $SiO_2$  ( $Et_2O$ ) Rf 0.9 det u.v.

5 Example 1

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine

A solution of the 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulphonyl-phenyl)-ethanone (233mg) and 2-aminopyridine (59mg) in dry acetonitrile was heated at reflux overnight. The reaction mixture was adsorbed onto silica and purified by flash chromatography eluting with ethyl acetate to afford the title compound as a cream solid (100mg).

10  $MH^+ = 367.2$

m.p. 198-200°

15 Example 2

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine

A solution of the 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulphonyl-phenyl)-ethanone (233mg) and 2-amino-3-methylpyridine (68mg) in dry acetonitrile (10ml) was heated at reflux overnight. The reaction mixture was adsorbed onto silica and purified by flash chromatography eluting with dichloromethane/methanol (19:1) to afford the title compound as a pale brown solid (61mg).

20  $MH^+ = 381$

m.p. 180-182°

25 Example 3

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-trifluoromethyl-imidazo[1,2-a]pyridine

A solution of 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulphonyl-phenyl)-ethanone (742mg), and 3-trifluoromethyl-pyridin-2-ylamine (324mg,) in dry acetonitrile containing potassium carbonate (276mg) was heated at reflux overnight. The reaction mixture was concentrated onto silica and purified by flash chromatography eluting with ethyl acetate, to give a yellow solid. Further

purification by recrystallisation from propan-2-ol yielded the title compound as yellow crystals (210mg).

m.p. 260-261°

Analysis: Found: C,57.7; H,3.0; N,6.2; S,7.3

5 C<sub>21</sub>H<sub>14</sub>F<sub>4</sub>N<sub>2</sub>O<sub>2</sub>S Requires: C,58.1; H,3.25; N,6.45; S,7.4%

MH<sup>+</sup> = 435

Tlc, SiO<sub>2</sub>, Rf 0.25, (ethyl acetate) detection u.v.

Example 4

3-(4-Fluoro-phenyl)-2-(4-methanesulphonyl)-7-methyl-imidazo[1,2-a]pyridine

10 A solution of the 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulphonyl-phenyl)-ethanone (233mg) and 2-amino-4-methylpyridine (68mg) in acetonitrile 10ml) was heated at reflux for 18 hours. The cooled reaction mixture was absorbed onto silica and the title compound obtained by flash chromatography, eluting with ethyl acetate /hexane (1/1), as a buff solid (105mg).

15 m.p.194-196°

MH<sup>+</sup> = 381

Tlc, SiO<sub>2</sub>, Rf 0.26, (ethyl acetate/hexane (2/1)) detection u.v.

Example 5

8-Chloro-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine

20 A suspension of 8-chloro-3-(4-fluoro-phenyl)-2-(4-methanesulfanyl-phenyl)-imidazo[1,2-a]pyridine (150mg) in methanol (8ml) and water (2ml) was treated with Oxone™ (561mg) and stirred for 2h at room temperature. The resulting suspension was treated with water (50ml) and extracted with ethyl acetate (2 x 50ml). The dried (MgSO<sub>4</sub>) extract was evaporated and the resulting solid was treated with boiling isopropanol (8ml) for (10min) cooled and filtered to give the title compound as a white solid (85mg).

25 m.p. 242-244°

Tlc SiO<sub>2</sub> (Et<sub>2</sub>O) RF 0.5 det u.v., KMnO<sub>4</sub>

30 MH<sup>+</sup> = 401

Example 63-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methanesulfanyl-imidazo[1,2-a]pyridine

5 A solution of 3-methylsulfanyl-pyridin-2-ylamine (140 mg) and 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone (371 mg) in acetonitrile (15ml) was heated at reflux overnight. The cooled reaction mixture was absorbed onto silica and the title compound obtained by flash chromatography eluting with ethyl acetate/cyclohexane (1/1) as a white solid (179 mg).

m.p. 224-226°

10  $MH^+ = 413$

Tlc,  $SiO_2$ , Rf 0.60 (ethyl acetate/cyclohexane(1/1)) detection u.v./ $KMnO_4$

Example 78-Bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine

15 A solution of 3-bromo-pyridin-2-ylamine<sup>3</sup> (173 mg) and 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone (371 mg) in acetonitrile (15ml) was heated at reflux overnight. On cooling to room temperature the title compound crystallised from solution and was isolated by filtration as a white solid (241 mg).

20 m.p 266-268°

$MH^+ = 446$

Analysis: Found : C,53.5;H,3.0;N,6.2;F,4.3;S,7.1

$C_{20}H_{14}BrFN_2O_2S$  Requires: C,53.9;H,3.2;N,6.3;F,4.3;S,7.2%

Tlc,  $SiO_2$ , Rf 0.61(Ethyl acetate/cyclohexane(2/1)) detection u.v.,  $KMnO_4$

25 <sup>3</sup> Ref: M.Malinowski,Bull. Soc. Chim. Belg. 1988, 97, 51

Example 88-Fluoromethyl-3-(4-fluoro-phenyl)-2-(4-methanesulphonyl-phenyl)-imidazo[1,2-a]pyridine

30 A solution of 3-(4-fluoro-phenyl)-2-(4-methanesulphonyl-phenyl)-imidazo[1,2-a]pyridine-8-methanol (200mg) in dichloromethane (10ml) was added to a cooled solution of diethylaminosulphur trifluoride (0.067 ml) in dichloromethane (4 ml) at -78° over 5 minutes. The solution was allowed to warm to room temperature over 30 minutes. Water (15 ml) was added cautiously with stirring, the organic phase was separated, dried ( $Na_2SO_4$ ) and absorbed onto silica. The title compound was obtained by flash chromatography eluting with ethyl

acetate/cyclohexane (1/1) as a white solid which was further purified by crystallisation from propan-2-ol (10 ml) yielding white crystals (85 mg).

m.p. 221-222°

$MH^+ = 399$

5 Analysis Found: C,63.1; H,3.9; N,6.8, F,9.4; S,8.1

$C_{21}H_{16}F_2N_2O_2S$  Requires: C,63.3; H,4.05; N,7.1, F,9.5; S,8.05%

Example 9

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-7,8-dimethyl-imidazo[1,2-a]pyridine

10 A solution of 3,4-dimethyl-pyridin-2-ylamine<sup>4</sup> (122 mg) and 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulphonyl-phenyl)-ethanone (371 mg) in acetonitrile (15ml) containing potassium carbonate (138 mg) was heated at reflux overnight. The cooled mixture was absorbed onto silica and the title compound obtained by flash chromatography eluting with ethyl acetate/cyclohexane (1/1) as a white 15 solid. Crystallisation from propan-2-ol (10 ml) yielded white crystals (136 mg).

m.p. 228-230°

$MH^+ = 395$

Analysis Found: C,66.6; H,4.7; N,6.9; F,4.8; S,8.2

$C_{22}H_{19}N_2FO_2S$  Requires: C,67.0; H,4.85; N,7.1; F,4.8; S8.1%

20 <sup>4</sup> Ref: W O Siegl, J Het. Chem. 1981, 18, 1613-18

Example 10

3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine-8-carbaldehyde

25 A solution of the [3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-methanol (500mg) and manganese (IV) oxide (1.32g) in chloroform (50ml) was heated at reflux for 16 hours. The cooled reaction mixture was filtered and the filtrate concentrated onto silica. The title compound was obtained by flash chromatography eluting with ethyl acetate/cyclohexane (4/1) as a bright yellow solid (315mg).

30  $MH^+ = 395$

Analysis Found: C,63.71; H,3.55; N,6.89; S,8.07;

$C_{21}H_{15}FN_2O_3S$  Requires: C,63.95; H,3.83; N,7.10; S,8.13%.

Example 115-Bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine

5 A solution of 3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine (380 mg) in chloroform (20 ml) was treated with solid N-bromosuccinimide (178 mg) in one portion at ambient temperature, and the resulting solution stirred overnight. Water (50 ml) was added and the organic phase collected, dried ( $\text{Na}_2\text{SO}_4$ ) and absorbed onto silica. The title compound was obtained by flash chromatography eluting with cyclohexane/ethyl acetate (1/1) as a white solid (106 mg).

10 m.p. 277-279° (dec)

$\text{MH}^+ = 461$

Tlc,  $\text{SiO}_2$ , Rf 0.22(Ethyl acetate/cyclohexane(1/1)) detection uv,  $\text{KMnO}_4$

Example 128-Acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine

15 A suspension of 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine (130mg) in methanol (8ml) and water (2ml) was treated with Oxone™ (436mg) and stirred for 3h at room temperature. The resulting suspension was treated with water (50ml) and extracted with ethyl acetate (50ml). The dried ( $\text{MgSO}_4$ ) extract was evaporated and the resulting solid was treated with boiling isopropanol (3ml) for (10min), cooled and filtered to give the title compound as a white solid (85mg).

20 m.p. 236-237°

25 Tlc  $\text{SiO}_2$  ( $\text{Et}_2\text{O}$ ) Rf 0.5 det u.v.,  $\text{KMnO}_4$

$\text{MH}^+ = 401$

Example 136-Bromo-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-8-methyl-imidazo[1,2-a]pyridine

30 A mixture of 1-amino-4-bromo-2-methylpyridine (500mg), 2-bromo-2-(4-fluoro-phenyl)-1-(4-methanesulfonyl-phenyl)-ethanone (1.0g) and acetonitrile (10ml) was refluxed under nitrogen for 20h and evaporated. The residue was triturated

with diethyl ether (20ml) for 5 min, cooled and filtered. The procedure was repeated to give the title compound as a beige powder (580mg).

$MH^+ = 461$

Tlc  $SiO_2$  ( $Et_2O$ ) Rf 0.6 detection u.v.,  $KMnO_4$

5

Example 14

8-Acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine

10 A solution of 3-acetyl-2-aminopyridine<sup>5</sup> (2.50g) and 2-bromo-2-(4-fluorophenyl)-1-(4-methanesulphonylphenyl)ethanone (6.82g) in acetonitrile (125ml) containing sodium bicarbonate (2.31g) was heated at reflux overnight. The mixture was filtered hot and the filtrate left to cool to room temperature. The title compound crystallised from solution and was isolated by filtration as a yellow solid (3.58g).

15 Tlc  $SiO_2$  Rf 0.34 (ethyl acetate/hexane, 1.3:1) detection u.v., iodine

$^1H$  NMR 3.04(3H,s, $CH_3SO_2-$ ), 3.16(3H,s, $CH_3CO-$ ), 6.90(1H,t,J=7.0Hz,H-6), 7.31(2H,t,J=8.8Hz) & 7.45(2H,dd,J= 5.2Hz,8.8Hz) -  $C_6H_4F-$ , 7.85(2H,d,J=8.4Hz) & 7.91(2H,d,J=8.4Hz) -  $C_6H_4SO_2$ , 7.93(1H,dd,J=1.1,7.0Hz, H-7), 8.02(1H,dd,J=1.1,7.0Hz, H-5).

20 <sup>5</sup> Ref: F.Trecourt *et al*, J. Chem. Soc., Perkin Trans.1 1990, 9, 2409-2415

Example 15

[3-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-methanol

25 A solution of 3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic acid methyl ester (1.85g) in dry tetrahydrofuran (130ml) was cooled to -78° and treated with diisobutylaluminium hydride (17.4ml;1.0M solution in dichloromethane). Once the addition was complete the mixture was allowed to warm up to 25° and stirring continued for 2 h. Methanol (80ml) was added and the mixture concentrated onto silica. The title compound was obtained by flash chromatography eluting with dichloromethane/ethanol/ammonia, 100/8/1, as a white foam (1.54g).

$MH^+ = 397$

Tlc ( $SiO_2$ ) Rf 0.28 (dichloromethane/ethanol/ammonia, 100/8/1) detection U.V.

Example 16(±) 1-[3-(4-fluoro-phenyl)-2-(4-methanesulphonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-ethan-1-ol

5 A solution of [3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridin-8-yl]-methanol (204 mg) in dry dichloromethane (10 ml) was cooled to -78°. A solution of diisobutylaluminium hydride (1.0 M in dichloromethane 1ml) was added dropwise and the mixture allowed to warm to ambient temperature over 30 minutes. Methanol (10 ml) was added in one portion and stirring continued for a further 30 minutes. The reaction mixture was absorbed onto 10 silica and the title compound obtained by flash chromatography eluting with ethyl acetate as a white solid (120 mg)

m.p.201-203°

T.I.c. SiO<sub>2</sub> Rf 0.45 (ethyl acetate) detection U.V.

15 Example 17 - Tablets

a)	Compound of the invention	5.0mg
	Lactose	95.0mg
	Microcrystalline Cellulose	90.0mg
20	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

25 The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b)	Compound of the invention	5.0mg
	Lactose	165.0mg
30	Pregelatinised Starch	20.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	<u>2.0mg</u>
	Compression weight	200.0mg

5 The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Example 18 - Capsules

a)	Compound of the invention	5.0mg
	Lactose	193.0mg
10	Magnesium Stearate	<u>2.0mg</u>
	Fill weight	200.0mg

15 The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b)	Compound of the invention	5.0mg
	Lactose	177.0mg
20	Polyvinylpyrrolidone	8.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	<u>2.0mg</u>
	Fill weight	200.0mg

25 The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

Example 19 - Syrup

a)	Compound of the invention	5.0mg
	Hydroxypropyl Methylcellulose	45.0mg
	Propyl Hydroxybenzoate	1.5mg
5	Butyl Hydroxybenzoate	0.75mg
	Saccharin Sodium	5.0mg
	Sorbitol Solution	1.0ml
	Suitable Buffers	qs
	Suitable flavours	qs
10	Purified Water to	10.ml

The hydroxypropyl methylcellulose is dispersed in a portion of hot purified water together with the hydroxybenzoates and the solution is allowed to cool to ambient temperature. The saccharin, sodium flavours and sorbitol solution are added to the bulk solution. The compound of the invention is dissolved in a portion of the remaining water and added to the bulk solution. Suitable buffers may be added to control the pH in the region of maximum stability. The solution is made up to volume, filtered and filled into suitable containers.

Example 20 - Injection Formulation

20		% w/v
	Compound of the invention	1.00
	Water for injections B.P. to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the pH remeasured and adjusted if necessary, to provide 10mg/ml of the compound of formula (I).

30 The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by

heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

5 Further sterile formulations are prepared in a similar manner containing 0.5, 2.0 and 5% w/v of the compound of formula (I), so as to provide respectively 5, 20 and 50mg/ml of the compound of formula (I).

#### Biological Data

10 Inhibitory activity against human COX-1 and COX-2 was assessed in COS cells which have been stably transfected with cDNA for human COX-1 and human COX-2. 24 Hours prior to experiment, COS cells were transferred from the 175cm<sup>2</sup> flasks in which they were grown, onto 24-well cell culture plates using the following procedure. The incubation medium, being Dulbecco's modified eagles medium (DMEM) to which had been added heat inactivated foetal calf serum (10%v/v), penicillin (100U /ml), streptomycin (100µg/ml) and geneticin (600µg/ml), was removed from a flask of confluent cells (1 flask at confluence contains approximately 1x10<sup>7</sup> cells). 10ml of phosphate buffered saline (PBS) was added to the flask to wash the cells. Having removed the PBS, cells were rinsed in 10ml trypsin for 20 seconds, after which the trypsin was removed and the flask placed in an incubator (37°) for 1-2 minutes until cells became loose. 15 The flask was then removed from the incubator and cells resuspended in 10ml of fresh incubation medium. The contents of the flask was transferred to a 250ml sterile container and the volume of incubation medium subsequently made up to 100ml. 1ml cell suspension was pipetted into each well of 4x24-well cell culture plates. The plates were then placed in an incubator (37°C, 95% air/5% CO<sub>2</sub>) overnight. If more than 1 flask was used, the cells were combined 20 before being dispensed into the 24-well plates.

25 Following the overnight incubation, the incubation medium was completely removed from the 24-well cell culture plates and replaced with 250µl fresh DMEM (37°C). Test compounds were made up to 250x the required test concentration in DMSO and were added to the wells in a volume of 1µl. Plates were then mixed gently by swirling and then placed in an incubator for 1 hour

(37°C, 95% air/5% CO<sub>2</sub>). Following the incubation period, 10µl of arachidonic acid (750µM) was added to each well to give a final arachidonic acid concentration of 30µM. Plates were then incubated for 15 minutes, after which the incubation medium was removed from each well of the plates and stored at -20°C, prior to determination of prostaglandin E<sub>2</sub> (PGE2) levels using enzyme immunoassay. The inhibitory potency of the test compounds was expressed as an IC<sub>50</sub> value, which is defined as the concentration of the compound required to inhibit the PGE2 release from the cells by 50%. The selectivity ratio of inhibition of COX-1 versus COX-2 was calculated by comparing respective IC<sub>50</sub> values.

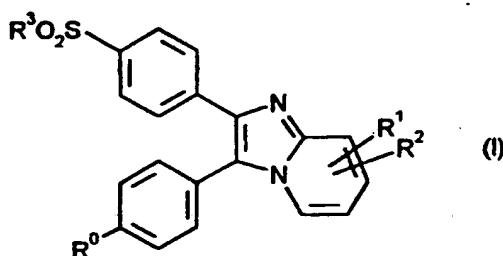
5

10 The following IC<sub>50</sub> values for inhibition of COX-2 and COX-1 were obtained for compounds of the invention:

Example No.	COX-2: IC <sub>50</sub> (nM)	COX-1: IC <sub>50</sub> (nM)
1	428	>100,000
2	54	>10,445
3	144	>100,000
4	159	>100,000
5	38	>100,000
6	212	>100,000
7	71	>100,000
8	38	>100,000
9	38	>100,000
10	476	>100,000
11	18	6,295
12	142	>100,000
13	275	>100,000
15	750	>100,000
16	650	>100,000

Claims

## 1. Compounds of formula (I)



and pharmaceutically acceptable derivatives thereof in which:

5

R⁰ represents halogen;

R¹ and R² are independently selected from H, halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted by one or more fluorine atoms, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>hydroxyalkyl, SC<sub>1-4</sub>alkyl, C(O)H or C(O)C<sub>1-4</sub>alkyl; and

10

R³ represents C<sub>1-4</sub>alkyl.

2. Compounds as claimed in claim 1 wherein R³ represents methyl.

3. Compounds as claimed in claim 1 or 2 wherein R⁰ represents fluorine.

4. Compounds as claimed in any one of claims 1 to 3 wherein R¹ represents H, chlorine, bromine, C<sub>1-4</sub>alkyl (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g. CH<sub>2</sub>F or CF<sub>3</sub>), C<sub>1-4</sub>hydroxyalkyl (e.g. CH<sub>2</sub>OH or CH(OH)CH<sub>3</sub>), SC<sub>1-4</sub>alkyl (e.g. SCH<sub>3</sub>), C(O)H or C(O)C<sub>1-4</sub>alkyl (e.g. C(O)CH<sub>3</sub>).

15

5. Compounds as claimed in any one of claims 1 to 4 wherein R² represents H, chlorine, bromine or C<sub>1-4</sub> alkyl (e.g. methyl).

20

6. Compounds as claimed in any one of claims 1 to 5 wherein R⁰ represents fluorine; R¹ represents H, chlorine, bromine, C<sub>1-4</sub>alkyl (e.g. methyl), methyl substituted by one to three fluorine atoms (e.g. CH<sub>2</sub>F or CF<sub>3</sub>), C<sub>1-4</sub>hydroxyalkyl (e.g. CH<sub>2</sub>OH or CH(OH)CH<sub>3</sub>), SC<sub>1-4</sub>alkyl (e.g. SCH<sub>3</sub>), C(O)H or C(O)C<sub>1-4</sub>alkyl (e.g. C(O)CH<sub>3</sub>); R² represents H, chlorine, bromine, or C<sub>1-4</sub>alkyl (e.g. methyl); and R³ represents methyl.

7. Compounds as claimed in any one of claims 1 to 6 wherein  $R^0$  represents fluorine;  $R^1$  represents H, chlorine, bromine, methyl,  $CH_2F$ ,  $CF_3$ ,  $SCH_3$ ,  $C(O)H$  or  $C(O)CH_3$ ;  $R^2$  represents H, bromine or methyl; and  $R^3$  represents methyl.

8. Compounds as claimed in any one of claims 1 to 7 wherein  $R^1$  is at the 5-position; and  $R^2$  is at the 7-position or, when  $R^1$  is other than H, the 5-, 6- or 7-position.

9. Compounds as claimed in any one of claims 1 to 8 wherein  $R^1$  is at the 8-position; and  $R^2$  is at the 7-position or, when  $R^1$  is  $C_{1-4}$ alkyl (e.g. methyl), the 5- or 7-position.

10. Compounds as claimed in any one of claims 1 to 9 wherein  $R^1$  represents  $C(O)CH_3$ .

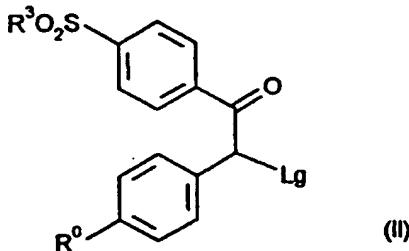
11. 8-Acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine and pharmaceutically acceptable derivatives thereof.

12. Compounds as claimed in any of claims 1 to 11 wherein the compound of formula (I) is in the form of a hydrochloride, hydrobromide or sulphate.

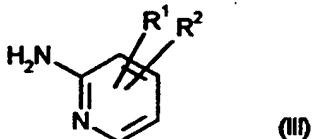
13. A process for the preparation of compound of formula (I) and pharmaceutically acceptable derivatives thereof as defined in any one of claims 1 to 12, which comprises:

(A) reacting a compound of formula (II)

20

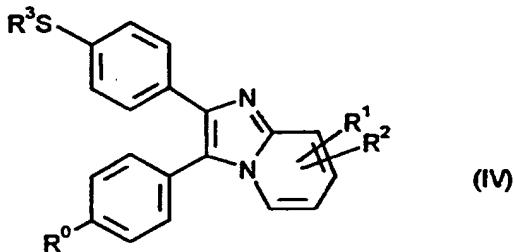


or a protected derivative thereof, wherein  $Lg$  represents a leaving group, with a compound of formula (III)



or a protected derivative thereof; or

5 (B) reacting a compound of formula (IV)



or a protected derivative thereof with an oxidising agent; or

(C) interconversion of a compound of formula (I) into another compound of formula (I); or

10 (D) deprotecting a protected derivative of compound of formula (I);

and optionally converting compounds of formula (I) prepared by any one of processes (A) to (D) into pharmaceutically acceptable derivatives thereof.

14. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 12 in admixture with one or more physiologically acceptable carriers or excipients.

15 15. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 12 for use in human or veterinary medicine.

20 16. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 12 for use in the treatment of a condition which is mediated by selective inhibition of COX-2

17. A method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative as defined in any one of Claims 1 to 5 12.

18. The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 12 for the manufacture of a therapeutic agent for the treatment of inflammatory disorders.

19. A method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of Claims 1 to 12. 10

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP 96/01438

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D471/04 A61K31/435 // (C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 455 924 (LEDNICKER) 15 July 1969 see column 2, line 10 - line 19; claim 1 -----	1,14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*'A' document defining the general state of the art which is not considered to be of particular relevance
- \*'E' earlier document but published on or after the international filing date
- \*'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*'O' document referring to an oral disclosure, use, exhibition or other means
- \*'P' document published prior to the international filing date but later than the priority date claimed

\*'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*'A' document member of the same patent family

1

Date of the actual completion of the international search

24 June 1996

Date of mailing of the international search report

05.07.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

# INTERNATIONAL SEARCH REPORT

I: International application No.

PCT/EP 96/01438

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 19 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Int'l Application No

PCT/EP 96/01438

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-3455924	15-07-69	BE-A-	710505	08-08-68

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER: \_\_\_\_\_**

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**